Pd-Catalyzed sp^2-sp cross-coupling reactions involving C-F bond activation of highly fluorinated nitrobenzene systems

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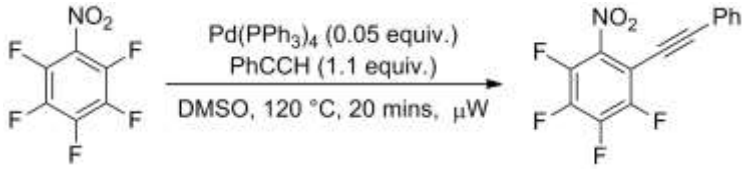

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Pd–Catalyzed sp^2–sp cross–coupling reactions involving C–F bond activation in highly fluorinated nitrobenzene systems

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Abstract— Direct and regioselective alkynylation of highly fluorinated nitrobenzene derivatives by palladium–catalyzed Sonogashira type processes is described, representing the first examples of metal–catalyzed sp^2–sp cross-coupling reactions involving C–F bond activation.

1. Introduction

Metal–catalyzed cross-coupling reactions of aryl halides with suitable organic or organometallic partners, such as boronic acids, Grignard reagents and alkene derivatives, are used extensively in organic synthesis as an important method for forming carbon–carbon bonds. Applications of cross-coupling processes to the pharmaceutical industry, drug development programs and natural product target synthesis are well documented and continue to increase.[1-3] Typically, aryl iodides and bromides are employed as the aromatic electrophilic coupling partner in Pd catalyzed coupling reactions because of the relative ease of oxidative addition of the metal catalyst into the carbon–halogen bond due to the relatively low C–I and C–Br bond strengths. Aryl chlorides are used less frequently whilst examples of metal–catalyzed C–F bond activation reactions are relatively rare because the C–F bond is the strongest single covalent bond to carbon[4] and, consequently, activation of C–F bonds by transition metal catalysts is a very challenging research goal, particularly in reactions involving highly fluorinated aromatic substrates.

Research into transition metal mediated C–F bond activation has been growing over the past decade although most of the available literature is concerned with the formation of stoichiometric metal–fluoride complexes, which may act as catalysts, or the functionalization of monofluoroaromatic systems to afford non–fluorinated products.[5,6] Braun has successfully carried out nickel–catalyzed Stille[7,8] and Suzuki[9] coupling reactions of several perfluoroheteroaromatic derivatives, pentafluoropyridine and 2,4,6-trifluoro-5-chloropyrimidine, respectively. Radius has also reported similar Suzuki cross–coupling reactions between octafluorotoluene and decafluorobiphenyl and various electron rich aryl boronic acid derivatives in which the C–F bond *para* to the trifluoromethyl or pentafluorophenyl group was activated and fluorine displaced by an aryl group.[10]

Perfluoroaromatic systems such as octafluorotoluene and decafluorobiphenyl are highly reactive towards nucleophilic attack, due to the presence of the highly electron withdrawing ring fluorine substituents and a large number of reactions between perfluoro- and highly fluorinated aromatic derivatives and a range of nucleophiles by S_NAr processes have been reported.[11] In particular, reactions involving Grignard or organolithium reagents can, in some cases, be useful methods for direct C–C bond formation although low regioselectivity, competing polysubstitution and substrate degradation can lead to very low yielding reactions in many cases.

In a recent publication,[12] we reported the first examples of palladium–catalyzed Suzuki-Miyaura sp^2–sp^2 cross-coupling reactions of a perfluorinated substrate, pentafluoronitrobenzene, using a conventional, readily available palladium catalyst, $Pd(PPh_3)_4$. The nitro group attached to the aryl ring not only helps to activate the system towards nucleophilic attack by the palladium catalyst, but also 'directs' oxidative addition to the *ortho* site. Crucially, reaction between the boronic acid derivative, base and pentafluoronitrobenzene does not occur in the absence of the palladium catalyst, indicating that oxidative addition of the palladium into the C–F bond is a key part of the reaction process. The mechanism of the oxidative addition step has some characteristics of an S_NAr type process, consistent with earlier observations by Kim and Yu[13] and Widdowson[14] concerning palladium–catalyzed cross coupling reactions involving monofluorinated aromatic systems.

Once oxidative addition has occurred, the aryl–palladium oxidative addition complex is, in principle, reactive

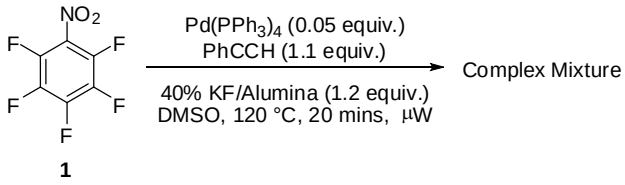
towards a range of substrates such as, for example, organo–stannane and organo–zinc reagents, alkynes and alkenes in Stille, Negishi, Sonogashira and Heck type processes, respectively. However, the highly nucleophilic nature of aryl tin and aryl zinc reagents may render these nucleophilic species incompatible for use with highly electrophilic fluorinated aromatic systems. Consequently, we envisaged that alkyne derivatives may be suitable coupling partners with which to further develop perfluoroaromatic C–F bond activation coupling chemistry.

In this paper, we describe sp^2–sp Sonogashira type cross coupling reactions involving carbon-fluorine bond activation. Whilst a limited number of Suzuki–Miyaura and Stille type processes of a suitable electrophilic fluoroaryl partner have been reported as outlined above, no sp–sp^2 cross–coupling reactions involving C–F activation have been described previously.

2. Results and discussion

In initial experiments, reaction of phenyl acetylene with pentafluoronitrobenzene **1** under similar conditions to those that we utilized for corresponding Suzuki–Miyaura cross–coupling processes was unsuccessful, affording tarry material from which no alkynylated product could be identified by ^{19}F NMR spectroscopic analysis of the product mixture. (Scheme 1)

Scheme 1. Attempted cross-coupling reaction of pentafluoro-nitrobenzene **1** with phenyl acetylene

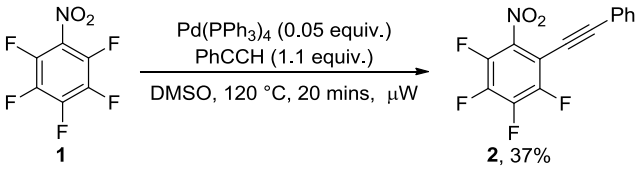


1

The fluoride ion was selected as the base because, in our previous investigations, conventional carbonate and amine bases were found to be unsuitable due to their tendency to undergo competing S_NAr processes with highly electrophilic polyfluoronitrobenzene systems. However, although Suzuki-Miyaura processes require a base to activate the boronic acid, in corresponding Sonogashira reactions the base is believed to assist with the abstraction of a proton from the alkyne derivative and in the neutralization of any acidic byproduct, in this case hydrogen fluoride.

As the oxidative addition of the palladium catalyst into pentafluoronitrobenzene does not involve the base, and that the fluoride ion displaced by this process can potentially assist with proton abstraction from the alkyne fragment, the C-F activation process was carried out in the absence of base. (Scheme 2)

Scheme 2. Successful cross-coupling reaction of pentafluoronitrobenzene **1** with phenylacetylene



1 **2**, 37%

In this case, complete conversion of pentafluoronitrobenzene **1** into alkynated derivative **2** was observed by ^{19}F NMR spectroscopic analysis of the crude reaction mixture, along with one equivalent of fluoride ion present (-150 ppm). The structure of **2** was confirmed by the presence of four resonances of equal intensity at –132.0, –145.6, –149.1 and –150.9 ppm in the ^{19}F NMR spectrum of the purified product, all of which exhibit appropriate mutual $^3J_{FF}$ coupling constants (21–22 Hz) consistent with the structure proposed. No cross–coupling reaction was observed in the absence of $Pd(PPh_3)_4$, confirming the catalytic nature of this process and the requirement of palladium insertion into the C–F bond as a preliminary step.

Despite the high efficiency of the coupling procedure, the isolated yield of **2** was lower than expected due to difficulties with product purification and subsequent decomposition of the product upon isolation. We postulate that that the reactivity of **2** as a Michael acceptor towards water in work up processes may be a possible decomposition pathway.

The sp–sp^2 alkynyl–aryl coupling process was found to be highly selective and afforded the alkynylated product arising from exclusive substitution of a fluorine atom *ortho* to the nitro group and is similar to the regioselectivity observed for corresponding Suzuki cross–coupling reactions of pentafluoronitrobenzene. A reaction mechanism is suggested in which oxidative addition of the palladium catalyst into the C–F bond *ortho* to the nitro group of **1** occurs initially by an S_NAr type process, as previously reported in related Suzuki–Miyaura coupling processes,[12] followed by coordination of the alkyne fragment to the palladium centre and the expulsion of the metal–bound fluoride ion. (Figure 1)

Interestingly, alkyne derivative **2** has been synthesized previously in low yield by an S_NAr process involving reaction of highly nucleophilic sodium phenylacetylide with pentafluoronitrobenzene in diethyl ether.[15] In this case, strong electronic interactions between the nitro group and the approaching nucleophile induce exclusive substitution *ortho* to the nitro group, although increasing the polarity of the solvent upon the addition of small quantities of THF was found to lead to preferential substitution to the *para* position. However, reactions involving highly fluorinated aromatic systems and phenyl acetylide derivatives can be difficult to control and, in several cases, dialkynylated

products are observed, even when using a large excess of perfluoroaromatic substrate.[15,16]

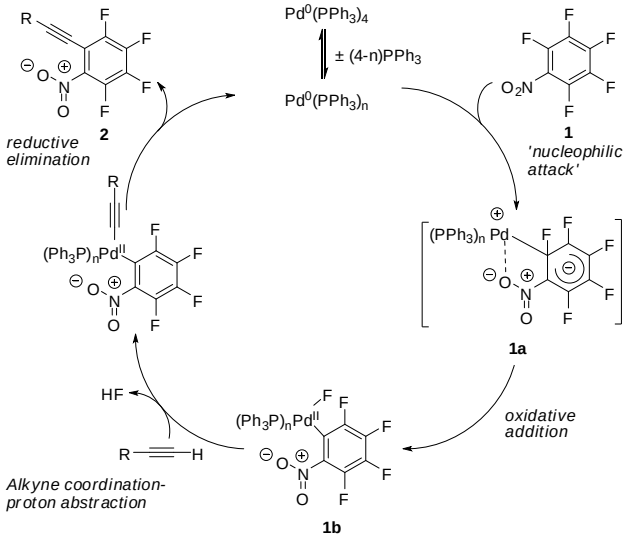
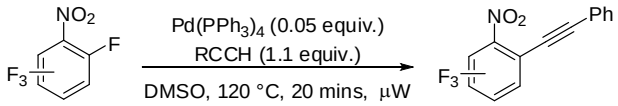


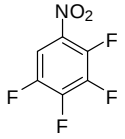
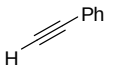
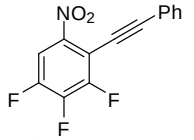
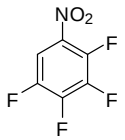
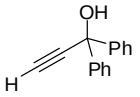
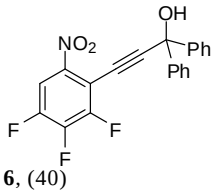
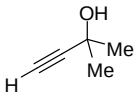
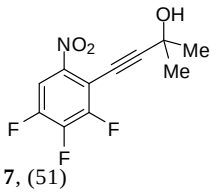
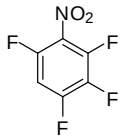
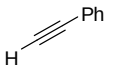
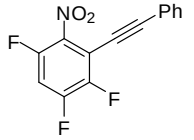
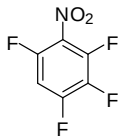
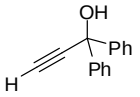
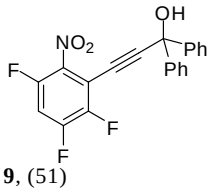
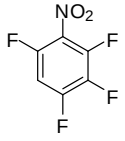
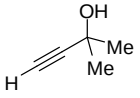
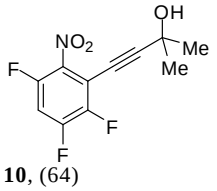
Figure 1. Proposed reaction mechanism

Analogous sp^2–sp coupling reactions of tetrafluorinated nitroaromatic systems **3**–**4** are shown in Table 1. These systems are, in principle, too acidic for use with organometallic reagents because ring metallation is preferred, as observed in reactions of less acidic substrates such as pentafluorobenzene with aryl lithium reagents. Indeed, we found that reaction of phenyl acetylide with tetrafluoronitrobenzene **3** in diethyl ether afforded a complex mixture of products and tarry material which could not be identified but, presumably, arose from deprotonation followed by elimination to benzyne intermediates and subsequent decomposition..

Complete conversion of tetrafluoronitrobenzene derivatives **3**–**4** into the corresponding alkynylated systems **5**–**10** was observed by ^{19}F NMR spectroscopic analysis of the respective crude reaction mixtures and, in each case, one equivalent of fluoride ion was also detected. Once again, the isolated yields of **5**–**10** were reduced due to problems with product isolation and decomposition, although the cross–coupling procedures themselves appear to be highly efficient, as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixtures. However, the palladium catalyzed processes reported here are far more effective for arylation of sites *ortho* to nitro groups in highly fluorinated systems bearing relatively acidic hydrogen atoms on the aromatic ring compared to conventional nucleophilic substitution processes involving carbon centred nucleophiles

Table 1. Palladium-catalyzed cross-coupling reactions of 2,3,4,5-tetrafluoronitrobenzene **3** and 2,3,4,6-tetrafluoronitrobenzene **4** with a range of alkyne derivatives



Electrophile	Nucleophile	Product, (Yield / %)
 **3**		 **5**, (48)
 **3**		 **6**, (40)
 **3**		 **7**, (51)
 **4**		 **8**, (51)
 **4**		 **9**, (51)
 **4**		 **10**, (64)

Reactions of tetrafluoronitrobenzene derivative **3** resulted in preferential alkynylation of the C–F bond *ortho* to the nitro group. The structure of **6** was confirmed by X–ray crystallography (Fig. 2) and NMR spectroscopy was used to confirm the identities of **5** and **7** by comparison of their respective ^{19}F NMR spectra with data obtained for **6**.

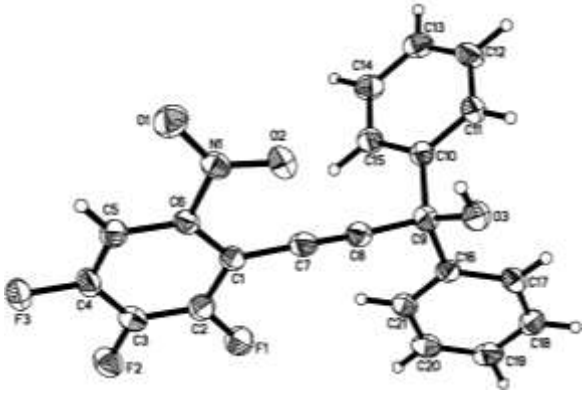


Figure 2. Molecular structure of **6**

For tetrafluoronitrobenzene derivative **4**, there are two C–F bonds located *ortho* to the nitro group at which directed oxidative addition of the palladium catalyst may occur but only products **8-10**, resulting from exclusive alkynylation at the 2–position, were observed. The structure of **8** is confirmed by the observation of an overlapping doublet of doublet of doublets at 7.1 ppm by ^{1}H NMR spectroscopy which displays two characteristic $^{3}J_{HF}$ coupling constants (9.2 Hz) and by the observation of two fluorine resonances at –126 and –135 ppm which were mutually split ($^{3}J_{FF}$ = 21.4 Hz) due to their respective *ortho* relationship. The structures of **9** and **10** were assigned accordingly.

These results are consistent with corresponding Suzuki–Miyaura processes reported previously[12] and may be explained by considering the relative activation of the two C–F bonds at the 2– and 6–positions towards oxidative addition. Although the activation of the C–F bond at the 6–position towards nucleophilic attack by the palladium catalyst is increased by the electron withdrawing *ortho* nitro group, the C–F bond at the 2–position is also further activated by an additional fluorine substituent attached to C-3 and oxidative addition occurs preferentially at this site. In earlier studies we found that Suzuki-Miyaura reactions involving similar Pd catalysed C-F activation processes of trifluoronitrobenzene substrates were very yielding and, consequently, analogous Sonagashira processes were not carried out here.

3. Conclusion

In conclusion, we have reported the first examples of metal–catalyzed cross-coupling sp^{2}–sp C–C bond forming reactions of fluoroaromatic systems in Sonogashira type processes involing C–F activation. The regioselectivity of alkynylation is consistent with corresponding Suzuki–Miyaura cross–coupling reactions, in which the nitro group is responsible for directing the palladium catalyst into the *ortho* C–F bond and, where there is a chioce, to the C–F bond site most activated towards nucleophilic substitution, suggesting that an S_NAr–type pathway is occuring.

4. Experimental Section

4.1 General

Analysis: Proton, carbon and fluorine nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) were recorded (^{1}H NMR, 500 MHz; ^{13}C NMR, 126 MHz; ^{19}F NMR, 470 MHz or ^{1}H NMR, 700 MHz; ^{13}C NMR, 176 MHz; ^{19}F NMR, 658 MHz) using solvent resonance as the internal standard (^{1}H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.36 ppm; ^{19}F NMR, $CFCl_3$ at 0.00 ppm). ^{1}H, ^{13}C and ^{19}F spectroscopic data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and assignment. Crystallographic data was recorded with a Rigaku R-Axis SPIDER IP diffractometer equipped with Cryostream (Oxford Cryosystems) low-temperature device at 120 K with graphite-monochromated MoK_{alpha}-radiation (λ = 0.71073 Å). Melting points were measured at atmospheric pressure and are uncorrected.

Chemicals and Solvents: Unless otherwise stated, commercially available reagents were used without purification. MeCN, DMF, THF and Toluene were dried by colorimetric titration whilst anhydrous DMSO and 1,4-dioxane were purchased from Sigma Aldrich. Hexane and DCM were purchased from Fischer and used without further purification. All microwave irradiated reactions were carried out in a Biotage Initiator™ Sixty microwave system (0-400 W at 2.45 GHz). Flash column chromatography was carried out using Fluorochem Silicagel LC60A (40-63 micron).

4.2 Coupling reactions of polyfluoronitrobenzene derivatives

4.2.1 General procedure

$Pd(PPh_3)_4$ (0.05 equiv.) was charged to a 0.5–2.0 ml microwave vial which was sealed and purged with argon to create an inert atmosphere. Dry, degassed DMSO (1.9 ml), phenyl acetylene (1.1 equiv.) and pentafluoronitrobenzene (1.0 equiv.) were added in sequence to the vial which was then heated to 120 °C for 20 minutes under microwave irradiation. The reaction mixture was cooled and filtered through an alumina plug with DCM as the eluent to remove inorganic and particulate material. The organic washings were concentrated *in vacuo*, poured onto water (100 ml) and extracted with DCM (3 × 100 ml). The organic fractions were combined, washed with water (100 ml) and dried ($MgSO_4$). Volatiles were removed *in vacuo* and the desired product was purified by either column chromatography using silica gel using a mixture of hexane and DCM (1:9) as the eluent or by Kugelrohr distillation.

***1,2,3,4-Tetrafluoro-5-nitro-6-(phenylethynyl)benzene* 2**

Reaction of $Pd(PPh_3)_4$ (0.102 g, 0.09 mmol), phenyl acetylene (0.132 g, 1.29 mmol) and pentafluoronitrobenzene (0.250 g, 1.17 mmol) afforded 1,2,3,4-tetrafluoro-5-nitro-6-(phenylethynyl)benzene (0.127 g, 37%) as a yellow solid; mp 111–112 °C; HRMS–ASAP *(m/z)*: (M^-) calcd for $C_{14}H_6F_4NO_2$ 295.0256; found 295.0252; R_f 0.3 (hexane/DCM, 1:9); ^{1}H NMR (700 MHz; $CDCl_3$): δ 7.38–7.41 (2H, m, H–Ar), 7.43–7.46 (1H, m, H–Ar), 7.55–7.58 (2H, m, H–Ar); ^{13}C NMR (126 MHz; $CDCl_3$): δ 73.9–74.0 (m, –C≡C–), 104.4–104.5 (m, –C≡C–), 105.5 (dd, $^2J_{CF}$ 18.7, $^3J_{CF}$ 1.9, C–6), 121.1 (s, C–Ar), 129.0 (s, C–Ar), 130.7 (s, C–Ar), 132.5 (s, C–Ar), 136.6–136.9 (m, C–5), 139.9–141.7 (m, C–F), 140.8–142.4 (m, C–F), 142.2–143.9 (m, C–F), 147.1–148.7 (m, C–F); ^{19}F NMR (658 MHz; $CDCl_3/CFCl_3$): δ –132.02 (1F, ddd, $^3J_{FF}$ 21.3, $^4J_{FF}$ 3.8, $^5J_{FF}$ 9.8, F–Ar), –145.64 (1F, ddd, $^3J_{FF}$ 21.5, $^6J_{FF}$ 6.2, $^5J_{FF}$ 9.8, F–Ar), –149.10 (1F, ddd, $^3J_{FF}$ 21.3, $^3J_{FF}$ 21.0, $^4J_{FF}$ 6.2, F–Ar).–150.85 (1F, ddd, $^3J_{FF}$ 21.5, $^3J_{FF}$ 21.0, $^4J_{FF}$ 3.8, F–Ar).

***1,2,3-Trifluoro-5-nitro-4-(phenylethynyl)benzene* 5**

Reaction of $Pd(PPh_3)_4$ (0.074 g, 0.06 mmol), phenyl acetylene (0.154 g, 1.51 mmol) and 2,3,4,5-tetrafluoronitrobenzene (0.255 g, 1.31 mmol) afforded 1,2,3-trifluoro-5-nitro-4-(phenylethynyl)benzene (0.176 g, 48%) as a yellow solid; mp 79–80 °C; HRMS–ASAP *(m/z)*: (M^-) calcd for $C_{14}H_6F_3NO_2$ 277.0351; found 277.0355; R_f 0.25 (hexane/DCM, 1:9); GC–MS *m/z* (% relative intensity, ion): 277 (7, M^+), 260 (38), 230 (21), 105 (100), 77 (62), 51 (6); ^{1}H NMR (700 MHz; $CDCl_3$): δ 7.39–7.46 (3H, m, H–Ar), 7.45–7.62 (2H, m, H–Ar), 7.88 (1H, ddd, $^3J_{HF}$ 9.4, $^4J_{HF}$ 6.8, $^5J_{HF}$ 2.1, H–6); ^{13}C NMR (126 MHz; $CDCl_3$): δ 76.2–76.3 (m, –C≡C–), 104.5–104.6 (m, –C≡C–), 108.0 (dd, $^2J_{CF}$ 17.5, $^3J_{CF}$ 3.9, C–4), 110.2 (dd, $^2J_{CF}$ 22.7, $^3J_{CF}$ 3.6, C–6), 121.8 (s, C–Ar), 128.8 (s, C–Ar), 130.3 (s, C–Ar), 132.5 (s, C–Ar), 143.8 (ddd, $^1J_{CF}$ 263, $^2J_{CF}$ 15.5, $^2J_{CF}$ 15.5, C–2), 144.4–144.5 (m, C–5), 149.5 (ddd, $^1J_{CF}$ 258, $^2J_{CF}$ 11.3, $^3J_{CF}$ 3.8, C–Ar), 152.4 (ddd, $^1J_{CF}$ 258, $^2J_{CF}$ 11.2, $^3J_{CF}$ 3.5, C–Ar); ^{19}F NMR (658 MHz; $CDCl_3/CFCl_3$): δ –125.01 (1F, ddd, $^3J_{FF}$ 20.6, $^4J_{FF}$ 8.1, $^5J_{FH}$ 2.1, F–3), –129.43 (1F, ddd, $^3J_{FF}$ 20.8, $^3J_{FH}$ 9.4, $^5J_{FF}$ 8.5, F–1), –149.39 (1F, ddd, $^3J_{FF}$ 20.8, $^3J_{FF}$ 20.6, $^4J_{FH}$ 6.8, F–2).

***1,1-Diphenyl-3-(2,3,4-trifluoro-6-nitrophenyl)prop-2-yn-1-ol* 6**

Reaction of $Pd(PPh_3)_4$ (0.076 g, 0.07 mmol), 1,1-diphenylprop-2-yn-1-ol (0.294 g, 1.41 mmol) and 2,3,4,5-tetrafluoronitrobenzene (0.254 g, 1.30 mmol) afforded 1,1-diphenyl-3-(2,3,4-trifluoro-6-nitrophenyl)prop-2-yn-1-ol (0.202 g, 40%) as a yellow solid; mp 88–89 °C; Anal. Calcd for $C_{21}H_{12}F_3NO_3$: C, 65.80; H, 3.16; N, 3.65. Found: C, 65.90; H, 3.21; N, 3.69; R_f 0.3 (hexane/DCM, 1:9); GC–MS *m/z* (% relative intensity, ion): 383 (0.5, M^+), 350 (10), 182 (9), 105 (100), 77 (30), 51 (3); ^{1}H NMR (700 MHz; $CDCl_3$): δ 3.01 (1H, s, –OH), 7.30 (2H, t, $^3J_{HH}$ 7.3, H–Ar), 7.37 (4H, dd, $^3J_{HH}$ 7.3, $^3J_{HH}$ 7.3, H–Ar), 7.61 (4H, d, $^3J_{HH}$ 7.3, H–Ar), 7.86-7.91 (1H, m, H–5); ^{13}C NMR (126 MHz; $CDCl_3$): δ 74.1–74.2 (m, –C≡C–), 75.5 (s, C–OH), 106.9–107.1 (m, C–1), 107.1–107.2 (m, –C≡C–), 110.1 (dd, $^2J_{CF}$ 22.6, $^3J_{CF}$ 3.5, C–5), 126.3 (s, C–Ar), 128.4 (s, C–Ar), 128.8 (s, C–Ar), 143.8 (ddd, $^1J_{CF}$ 264, $^2J_{CF}$ 15.3, $^2J_{CF}$ 15.3, C–3), 143.9 (s, C–Ar), 144.2–144.4 (m, C–6), 149.9 (ddd, $^1J_{CF}$ 258, $^2J_{CF}$ 11.2, $^3J_{CF}$ 3.8, C–F), 152.9 (ddd, $^1J_{CF}$ 258, $^2J_{CF}$ 10.5, $^3J_{CF}$ 3.2, C–F); ^{19}F NMR (658 MHz; $CDCl_3$; $CFCl_3$): δ –124.27 (1F, dd, $^3J_{FF}$ 20.7, $^4J_{FF}$ 8.6, F–2), –128.21 (1F, ddd, $^3J_{FF}$ 20.7, $^3J_{FH}$ 8.5, $^4J_{FF}$ 8.6, F–4), –148.78 (1F, ddd, $^3J_{FF}$ 20.7, $^3J_{FF}$ 20.7, $^4J_{FH}$ 6.7, F–3).

Crystal data for ***6***: $C_{21}H_{12}F_3NO_3$, M = 383.32, monoclinic, space group P $2_1/n$, a = 14.4535(11), b = 6.2011(5), c = 19.5369(14) Å, β = 106.78(1)°, U = 1676.5(2) Å^3, F(000) = 784, Z = 4, D_c = 1.519 mg m^{-3}, μ = 0.124 mm^{-1} (Mo-Kα, λ = 0.71073 Å), T = 120(1)K. 13464 reflections (2.07 ≤ θ ≤ 27.5°) were collected on a Bruker SMART-CCD 6K diffractometer (ω-scan, 0.3°/frame) yielding 3846 unique data (R_{merg} = 0.0671). The structure was solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXL[18] and OLEX2[19] software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically. Final $wR_2(F^2)$ = 0.1126 for all data (301 refined parameters), conventional R (F) = 0.0545 for 2229 reflections with I ≥ 2σ, GOF = 1.003. The largest peak on the residual map is 0.30 e/Å^3. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-895941.

***2-Methyl-4-(2,3,4-trifluoro-6-nitrophenyl)but-3-yn-2-ol* 7**

Reaction of $Pd(PPh_3)_4$ (0.074 g, 0.06 mmol), 1,1-dimethylprop-2-yn-1-ol (0.122 g, 1.46 mmol) and 2,3,4,5-tetrafluoronitrobenzene (0.249 g, 1.28 mmol) afforded 2-methyl-4-(2,3,4-trifluoro-6-nitrophenyl)but-3-yn-2-ol (0.246 g, 69%) as a yellow solid which decomposed upon heating; Anal. Calcd for $C_{11}H_8F_3NO_3$: C, 50.98; H, 3.11; N, 5.40. Found: C, 51.15; H, 3.15; N, 5.73; R_f 0.4 (hexane/DCM, 1:9); ES^+–MS *m/z* (% relative intensity, ion): 282 (100, $[M + Na]^+$), 220 (30), 189 (18), 79 (34); ^{1}H NMR (700 MHz; $CDCl_3$): δ 1.65 (6H, s, $–CH_3$), 2.34 (1H, s, –OH), 7.80–7.85 (1H, m, H–Ar); ^{13}C NMR (126 MHz; $CDCl_3$): δ 31.1 (s, $–CH_3$), 66.1 (s, C–OH), 69.2–69.3 (m, –C≡C–), 107.2 (dd, $^2J_{CF}$ 17.2, $^3J_{CF}$ 4.3, C–1), 109.2–109.3 (m, –C≡C–), 110.2 (dd, $^2J_{CF}$ 22.6, $^3J_{CF}$ 3.5, C–5), 143.7 (dt, $^1J_{CF}$ 263, $^2J_{CF}$ 15.4, C–3), 144.6-144.8 (m, C–6), 149.9 (ddd, $^1J_{CF}$ 258, $^2J_{CF}$ 11.1, $^3J_{CF}$ 3.8, C–F), 152.9 (ddd, $^1J_{CF}$ 258, $^2J_{CF}$ 11.3, $^3J_{CF}$ 3.6, C–F); ^{19}F NMR (658 MHz; $CDCl_3/CFCl_3$): δ –125.05 (1F, dd, $^3J_{FF}$ 20.4, $^4J_{FF}$ 8.6, F–2), –128.98 (1F, ddd, $^3J_{FF}$ 20.6, $^3J_{FH}$ 8.9, $^4J_{FF}$ 8.6, F–4), –149.31 (1F, ddd, $^3J_{FF}$ 20.6, $^3J_{FF}$ 20.4, $^4J_{FH}$ 6.7, F–3).

***1,2,5-Trifluoro-4-nitro-3-(phenylethynyl)benzene* 8**

Reaction of $Pd(PPh_3)_4$ (0.076 g, 0.07 mmol), phenyl acetylene (0.127 g, 1.24 mmol) and 2,3,4,6-tetrafluoronitrobenzene (0.253 g, 1.29 mmol) afforded 1,2,5-trifluoro-4-nitro-3-(phenylethynyl)benzene (0.151 g, 44%) as a yellow solid; mp 123–124 °C; HRMS–ASAP *(m/z)*: (M^-) calcd for $C_{14}H_6F_3NO_2$ 277.0351; found 277.0345; R_f 0.2 (hexane/DCM, 1:9); GC–MS *m/z* (%

relative intensity, ion): 277 (1, M^+), 260 (22), 230 (18), 105 (100), 77 (66), 51 (8); ^{1}H NMR (700 MHz; $CDCl_3$): δ 7.12 (1H, ddd, $^3J_{HF}$ 9.2, $^3J_{HF}$ 9.2, $^4J_{HF}$ 6.3, H–6), 7.38–7.42 (2H, m, H–Ar), 7.43–7.46 (1H, m, H–Ar), 7.57–7.59 (2H, m, H–Ar); ^{13}C NMR (126 MHz; $CDCl_3$): δ 75.2–75.3 (m, –C≡C–), 104.8–104.9 (m, –C≡C–), 106.7 (dd, $^2J_{CF}$ 25.4, $^2J_{CF}$ 22.4, C–6), 111.0 (d, $^2J_{CF}$ 16.7, C–3), 121.1 (s, C–Ar), 128.8 (s, C–Ar), 130.5 (s, C–Ar), 132.5 (s, C–Ar), 136.7–137.0 (m, C–4), 147.5 (ddd, $^1J_{CF}$ 256, $^2J_{CF}$ 14.3, $^4J_{CF}$ 4.1, C–2), 150.3 (ddd, $^1J_{CF}$ 261, $^3J_{CF}$ 11.6, $^4J_{CF}$ 4.0, C–5), 151.7 (ddd, $^1J_{CF}$ 259, $^2J_{CF}$ 13.9, $^3J_{CF}$ 12.3, C–1); ^{19}F NMR (658 MHz; $CDCl_3$/$CFCl_3$): δ –122.21 (1F, ddd, $^3J_{FH}$ 9.2, $^4J_{FF}$ 6.4, $^5J_{FF}$ 13.0, F–5), –126.13 (1F, ddd, $^3J_{FF}$ 21.4, $^3J_{FH}$ 9.2, $^4J_{FF}$ 6.4, F–1), –134.66 (1F, ddd, $^3J_{FF}$ 21.4, $^4J_{FH}$ 6.3, $^5J_{FF}$ 13.0, F–2).

***1,1-Diphenyl-3-(2,3,5-trifluoro-6-nitrophenyl)prop-2-yn-1-ol* 9**

Reaction of $Pd(PPh_3)_4$ (0.076 g, 0.06 mmol), 1,1-diphenylprop-2-yn-1-ol (0.297 g, 1.43 mmol) and 2,3,4,6-tetrafluoronitrobenzene (0.254 g, 1.30 mmol) afforded 1,1-diphenyl-3-(2,3,5-trifluoro-6-nitrophenyl)prop-2-yn-1-ol (0.255 g, 50%) as a viscous yellow liquid; HRMS–ASAP *(m/z)*: (M^-) calcd for $C_{21}H_{12}F_3NO_3$ 383.0753; found 383.0769; R_f 0.3 (hexane/DCM, 1:9); ^{1}H NMR (700 MHz; $CDCl_3$): δ 3.04 (1H, s, –OH), 7.13 (1H, ddd, $^3J_{HF}$ 9.2, $^3J_{HF}$ 9.2, $^4J_{HF}$ 6.4, H–Ar), 7.29–7.32 (2H, m, H–Ar), 7.35–7.38 (4H, m, H–Ar), 7.59–7.62 (4H, m, H–Ar); ^{13}C NMR (126 MHz; $CDCl_3$): δ 73.0–73.1 (m, –C≡C–), 75.4 (s, C–OH), 107.4–107.5 (m, –C≡C–), 107.4 (dd, $^2J_{CF}$ 25.4, $^2J_{CF}$ 22.4, C–6), 110.1 (ddd, $^2J_{CF}$ 18.2, $^3J_{CF}$ 3.1, $^3J_{CF}$ 1.1, C–3), 126.2 (s, C–Ar), 128.5 (s, C–Ar), 128.8 (s, C–Ar), 136.6–136.8 (m, C–4), 143.6 (s, C–Ar), 147.9 (ddd, $^1J_{CF}$ 256, $^2J_{CF}$ 14.3, $^4J_{CF}$ 4.0, C–2), 150.4 (ddd, $^1J_{CF}$ 260, $^3J_{CF}$ 11.4, $^4J_{CF}$ 4.0, C–5), 151.9 (ddd, $^1J_{CF}$ 261, $^2J_{CF}$ 14.2, $^3J_{CF}$ 12.5, C–1); ^{19}F NMR (658 MHz; $CDCl_3$/$CFCl_3$): δ –121.54 (1F, ddd, $^3J_{FH}$ 9.2, $^4J_{FF}$ 6.6, $^5J_{FF}$ 13.1, 5-F), –125.38 (1F, ddd, $^3J_{FF}$ 21.4, $^3J_{FH}$ 9.2, $^4J_{FF}$ 6.6, 1-F), –133.84 (1F, ddd, $^3J_{FF}$ 21.4, $^4J_{FH}$ 6.4, $^5J_{FF}$ 13.1, 2-F).

***2-Methyl-4-(2,3,5-trifluoro-6-nitrophenyl)but-3-yn-2-ol* 10**

Reaction of $Pd(PPh_3)_4$ (0.078 g, 0.07 mmol), 1,1-dimethylprop-2-yn-1-ol (0.115 g, 1.41 mmol) and 2,3,4,6-tetrafluoronitrobenzene (0.254 g, 1.37 mmol) afforded 2-methyl-4-(2,3,5-trifluoro-6-nitrophenyl)but-3-yn-2-ol (0.219 g, 58%) as a yellow solid which decomposed upon heating; HRMS–ASAP *(m/z)*: (M^-) calcd for $C_{11}H_8F_3NO_3$ 259.0456; found 259.0459; R_f 0.2 (hexane/DCM, 1:9); ^{1}H NMR (700 MHz; $CDCl_3$): δ 1.61 (6H, s, –CH_3), 2.63 (1H, s, –OH), 7.12 (1H, ddd, $^3J_{HF}$ 9.2, $^3J_{HF}$ 9.2, $^4J_{HF}$ 6.4, H–Ar); ^{13}C NMR (126 MHz; $CDCl_3$): δ 30.9 (s, –CH_3), 66.0 (s, C–OH), 68.4–68.5 (m, –C≡C–), 107.1 (dd, $^2J_{CF}$ 25.3, $^2J_{CF}$ 22.5, C–4), 109.5–109.6 (m, –C≡C–), 110.2 (ddd, $^2J_{CF}$ 18.3, $^3J_{CF}$ 3.3, $^3J_{CF}$ 1.5, C–1), 136.9–137.2 (m, C–6), 147.6 (ddd, $^1J_{CF}$ 256, $^2J_{CF}$ 14.2, $^4J_{CF}$ 4.0, C–2), 150.2 (ddd, $^1J_{CF}$ 259, $^3J_{CF}$ 11.5, $^4J_{CF}$ 4.0, C–5), 151.8 (ddd, $^1J_{CF}$ 259, $^2J_{CF}$ 13.9, $^3J_{CF}$ 12.2, C–3); ^{19}F NMR (658 MHz; $CDCl_3$/$CFCl_3$): δ –122.22 (1F, ddd, $^3J_{FH}$ 9.1, $^4J_{FF}$ 6.4, $^5J_{FF}$ 13.1, F–5), –125.95 (1F, ddd, $^3J_{FF}$ 21.3, $^3J_{FH}$ 9.2, $^4J_{FF}$ 6.4, F–1), –134.69 (1F, ddd, $^3J_{FF}$ 21.3, $^4J_{FH}$ 6.3, $^5J_{FF}$ 13.1, F–2).

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